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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/126,559	07/30/98	CAPON D	50130-E/JPW/

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ALBERT WAI KAT CHAN
COOPER & DUNHAM
1185 AVENUE OF THE AMERICAS
NEW YORK NY 10036

EXAMINER	
BRUMBACK, B	

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 01/10/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/126,559	Capon et al.
Examiner	**Group Art Unit**
Brenda Brumback	1643

☒ Responsive to communication(s) filed on *Dec 1, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 4, 8, 20, 25, 37, 40, 55-59, 62, 77, 91, 94, and 108-111* is/are pending in the application.

Of the above, claim(s) *20, 25, 59, 62, 77, 91, 94, and 108-111* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 4, 8, 37, 40, and 55-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

2. The Preliminary Amendment filed 07/30/98 has been entered as Paper # 4. Claims 2, 3, 5-7, 9-19, 21-24, 26-36, 38, 39, 41-54, 60, 61, 63-76, 78-90, 92, 93, and 95-107 were canceled. Pending claims are 1, 4, 8, 20, 25, 37, 40, 55-59, 62, 77, 91, 94, and 108-111.

Note: Claim 81 was both canceled in Paper # 4 and subsequently listed as still pending (see line 5 of the first full paragraph). For purposes of examination, claim 81 has been considered to have been canceled. Clarification is required.

Election/Restriction

3. Applicant's election with traverse of Group I, claims 1, 4, 8, 37, 40, and 55-58, in Paper No. 8 is acknowledged. The traversal is on the grounds that Groups I-IV are interrelated because they all relate to a resistance test vector and are therefore not independent inventions. This is not found persuasive because, while the methods of Group I and III may require the test vector of Group II and IV respectively, the search for the methods of Groups I and III is not required for the vectors of Groups II and IV. Furthermore, the structure of the Flaviviridae test vectors of

Group II which contain a flavivirus gene, are distinct and different from the Herpesviridae test vector of Group IV, which contains a herpesvirus gene. While each of the test vectors may be used as resistance test vectors, their functions, as well as their structures, are different because they are used for determining drug resistance for different viruses. Additionally, the vectors of Groups II and IV may be used in processes additional to and independent from the methods of Groups I and III, as was outlined in Paper # 7 (see page 3, first paragraph of the page). For these reasons, the inventions are determined to be both independent and distinct.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20, 25, 59, 62, 77, 91, 94, and 108-111 are withdrawn from consideration ad drawn to a nonelected invention. Claims 1, 4, 8, 37, 40, 55-58 are under examination.

Drawings

4. The Drawings filed 07/30/98 have been approved.

Information Disclosure Statement

5. The Information Disclosure Statement (IDS) filed 02/10/99 has been entered as Paper # 6. A signed copy is attached hereto.

Specification

6. The specification is objected to because of the following informalities. On page 42, at lines 7, it appears that "is this" is a typographical error for "this is". At lines 12 and 18, the article "a" should be deleted to correct the grammar.

Claim Rejections - 35 USC § 112

7. Claims 1, 4, 8, 37, 40, and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 37 are drawn to methods for determining susceptibility for an HCV antiviral drug comprising introducing a resistance test vector comprising a patient-derived segment which comprises a hepatitis C virus (HCV) gene and an indicator gene into a host cell. The preamble of each of the claims is unclear as to what is being tested for susceptibility. For clarification, it is suggested that "for" be deleted from line 1 in each of the claims and that a phrase such as "of a hepatitis C virus strain" or "of a patient-derived viral strain" or other comparable phrase be inserted in line 1 after "susceptibility" for clarification.

Claims 1 and 37 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are measuring expression of the indicator gene in a target cell in the absence of an HCV antiviral drug and a correlation step. Also, the syntax of the claim renders the sequence of steps confusing because it is not clear what

is to be compared. Additionally, it is unclear how in step (c) expression of the indicator gene in a target cell in the presence of an antiviral drug can be measured if the drug is not present in either steps (a) and (b) or in step (b). It is suggested that the claim be amended to recite something such as,

(c) measuring expression of the indicator gene in a target cell in the absence of an HCV antiviral drug;

(d) measuring expression of the indicator gene in a target cell, wherein an HCV antiviral drug is present at steps (a) - (b) or at step (b); and

(e) comparing the expression of the indicator gene from (d) with the expression of the indicator gene from (c),

wherein a reduction in expression of the indicator gene in (d), as compared to (c), is indicative of susceptibility to the antiviral drug.

Claims 4 and 40 recite genes encoding C, E1, E2, NS2, NS3, NS4, or NS5. It is suggested for clarification that the claim be amended to insert -- proteins of HCV -- at the end of the claim. It is also suggested that claim 1 be amended to insert -- (HCV) -- in line 5 immediately after "hepatitis C virus" and that all subsequent occurrences of hepatitis C virus be changed to HCV for consistency (see claim 37, line 5).

Claim 8 recites "IRES". Immediately preceding the first occurrence of the acronym, the full name -- internal ribosome entry site -- should be inserted with parentheses around the abbreviation.

Claim 8 is rejected as depending from a canceled claim. Correction is required. It is suggested that claim 8 either be canceled or rewritten in independent form incorporating all limitations of the base claims or that claim 8 be rewritten to recite the limitations of claim 5 and to depend from claim 1. For purposes of examination, claim 8 has been interpreted to include all limitations of base claim 1 and canceled claim 5.

8. Claims 1, 4, 8, 37, 40 and 55-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determination of antiviral drug susceptibility wherein the antiviral drug is present in steps (a) and (b) or in step (b), does not reasonably provide enablement for determination of antiviral drug susceptibility when the drug is present only at step (c). Step (c) is drawn to measuring expression of the indicator gene in a target host cell; without the antiviral drug being present in either step (a) wherein the resistance test vector is introduced into the host cell or in step (b) wherein the host cell is cultured, one of skill in the art would be unable to measure a reduction in expression of the indicator gene in step (c). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 1, 4, 8, 55, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerna et al. (Journal of Clinical Microbiology, 1995, of record as Exhibit 6 in Paper # 6) in view of Lu et al. (Proc. Natl. Acad. Sci, 1996, of record as Exhibit 14 in Paper # 6) and Wang et al. (Journal of Virology, 1993, of record as Exhibit 21 in Paper # 6)..

The claimed invention is drawn to a method for determining susceptibility of an HCV strain for an antiviral drug comprising introducing a resistance test vector comprising a patient-derived HCV gene and an indicator gene into a host cell, culturing the host cell, and comparing expression of the indicator gene in the presence of an antiviral drug with expression in the absence of the drug. Dependent claims recite the additional limitations of the resistance test vector comprising genes encoding the C, E1, E2, NS2, NS3, NS4 or NS5 proteins of HCV; the patient-derived HCV gene comprising an internal ribosome entry site (IRES); and recite methods for determining HCV antiviral drug resistance in an infected patient comprising developing a standard curve of drug susceptibility for the antiviral drug and comparing the measured susceptibility to the standard curve as an indication of HCV antiviral drug resistance in the HCV-infected patient, or by comparing HCV antiviral drug susceptibilities in the same patient measured at a first and a later time as an indication of the development or progression of viral drug resistance in the patient.

Gerna et al. teach methods for determining susceptibility of human cytomegalovirus (HCMV) to antiviral drugs. Gerna et al. teach conventional methods for determination of drug susceptibility as comprising a plaque reduction assay in susceptible cell culture (immediate early antigen or IEA plaque assay) in the presence of the antiviral drug (ganciclovir or foscarnet) and comparison of the titer of the virus to a standard curve of drug susceptibility determined from control virus strains (see the entire document and especially page 738, the paragraph bridging columns 1 and 2, and the first sentence of the second paragraph in column 2). Gerna et al. teach that antiviral drug susceptibility testing is important because the use of antiviral agents can result in emergence of drug-resistant virus strains (see page 738, first paragraph). The methods described by Gerna et al. differ from the claimed methods in that they do not teach determination of drug susceptibility for HCV and they do not teach the use of resistance test vectors.

Lu et al. teach that HCV does not replicate in cell cultures to any appreciable titer. Lu et al. teach that this has hindered efforts to develop HCV-specific antiviral drugs (see page 1412, column 2, second paragraph). Lu et al. teach that certain RNA viruses, including HCV, have developed the mode of translation by IRES elements, which allows entry of the translational machinery into mRNAs without recognition of a 5'-end cap structure (see the paragraph bridging pages 1415 and 1416). Lu et al. teach that a chimeric polio/HCV virus which incorporates the HCV IRES, an HCV core (C) segment, and poliovirus segments productively infects cell culture, thereby allowing for HCV antiviral drug testing. Lu et al. teach that the use of the chimeric virus,

however, is limited to detection of HCV antiviral agents which target the 5' NTR or core protein (see page 1412, column 2, third paragraph).

Wang et al. teach methods for construction of vectors incorporating HCV-derived segments which comprise an IRES and an indicator gene (chloramphenicol acetyltransferase [CAT] or luciferase [LUC]) (see pages 3338, *Materials and Methods*, first three paragraphs). Wang et al. teach introduction of the HCV-derived segments into cells by transfection, incubation of the transfected cells in culture, and measurement of expression of the indicator gene as indicative of viral translation (see page 3339, column 2, third full paragraph; page 3340, column 2, last paragraph; and page 3341, column 1, first paragraph).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used the transfection methods taught by Wang et al. as a substitute for the plaque reduction assay taught by Gerna et al. in order to enable HCV antiviral susceptibility testing, either for elucidation of new HCV antiviral agents, as suggested by Lu et al., or for determination of drug susceptibility or developing resistance in a particular patient, as suggested by Gerna et al. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the methods taught by Wang, rather than the chimeric virus taught by Lu et al., in order to expand testing to antiviral agents in addition to those which target the 5'NTR or C protein of HCV.

b. Claims 37, 40, 56, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerna et al. in view of Lu et al. and Wang et al., as applied to claims 1, 4, 8, 55, and 57 above, and further in view of Hirowatari et al. (Analytical Biochemistry, 1995, of record as Exhibit 10 in Paper # 4).

The claimed invention is drawn to a method for determining susceptibility of an HCV strain for an antiviral drug comprising introducing a resistance test vector comprising a patient-derived HCV gene and a nonfunctional indicator gene into a host cell, culturing the host cell, and comparing expression of the indicator gene in the presence of an antiviral drug with expression in the absence of the drug. Dependent claims recite the additional limitations of the resistance test vector comprising genes encoding the C, E1, E2, NS2, NS3, NS4 or NS5 proteins of HCV and methods for determining HCV antiviral drug resistance in an infected patient comprising developing a standard curve of drug susceptibility for the antiviral drug and comparing the measured susceptibility to the standard curve as an indication of HCV antiviral drug resistance in the HCV-infected patient, or by comparing HCV antiviral drug susceptibilities in the same patient measured at first and later times as an indication of the development or progression of drug resistance in the patient.

As described *supra,* Gerna et al. teach methods for determining resistance to an antiviral drug comprising determining the susceptibility of a patient-derived isolate to the antiviral drug and comparison of the determined susceptibility to a standard curve. Lu et al. teach methods for testing HCV isolates in otherwise nonpermissive cells by incorporation of the HCV IRES element

and C protein with poliovirus segments into a chimeric virus. Wang et al. teach methods of construction of vectors comprising HCV segments which include the IRES element and an indicator gene, transfection of cells with the vectors, incubation of the transfected cells, and measurement of expression of the indicator gene. The claimed invention differs from the methods of Gerna et al. in view of Lu et al. and Wang et al. in the recitation of a nonfunctional indicator gene. A nonfunctional indicator gene is understood to mean one which is not efficiently expressed in a packaging host cell transfected with the resistance test vector until it is converted into a functional indicator gene through the action of one or more of the patient-derived HCV segment products, as is defined at page 33, lines 3-12, of the disclosure.

Hirowatari et al. teach a method for testing antiviral activity of HCV proteinase inhibitors comprising construction of plasmids encoding a reporter gene, the proteinase enzyme gene, and the substrate gene which are simultaneously transfected into cells in culture. Hirowatari et al. teach the reporter plasmid as containing the CAT gene downstream of an enhancer/promoter sequence derived from human T-cell leukemia virus type 1 (HTLV-1) long terminal repeat (LTR). Hirowatari et al. teach the substrate expression plasmid as a triple chimera comprising HCV NS2, the substrate polypeptide, and the Tax1 protein of HTLV-1. Hirowatari et al. teach that the Tax1 transactivates the expression of the CAT gene through the enhancer sequence of HTLV-1 LTR only after it is released from the chimera by HCV proteinase-dependent cleavage (see page 113, abstract, and the paragraph bridging pages 114 and 115). Hirowatari et al. teach that this system

allows for safe *in vivo* testing of antiviral agents without risk of exposure to infectious, pathogenic virus (see page 113, the paragraph bridging columns 1 and 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a nonfunctional indicator gene, as taught by Hirowatari et al., as the indicator gene in the methods taught by Gerna et al. in view of Lu et al. and Wang et al., as an alternative indicator of viral susceptibility to antiviral agents without the potential for hazardous exposure to infectious virus.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Paula Hutzell whose telephone number is (703) 308-4310. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
January 6, 2000

Brenda Brumback
BRENDA BRUMBACK
PATENT EXAMINER